8 Relapsed Osteosarcoma Trial Concepts to Match the Complexity of the Disease

Damon R. Reed, Pooja Hingorani, and Peter M. Anderson

Abstract

Osteosarcoma relapses not only herald a very poor prognosis but also opportunities to treat this genetically diverse complex cancer in new ways. This review will attempt to show that the field is a rapidly evolving one in which not only cytotoxic agents but also local control strategies and the immune system can be harnessed to improve the prognosis of relapsed patients. The molecular heterogeneity and the difficulty of effectively treating most common patterns of relapse with surgery and/or radiation (lung and/or bone metastases) have been responsible for a wide variety of approaches to learning whether agents are active against osteosarcoma. This chapter will highlight past, current, and potential future approaches to provide more effective systemic therapy for the problem of recurrent metastases of osteosarcoma. These include single-agent trials with a wide variety of agents, radiopharmaceuticals, and immune therapies. Finally, how such efforts are integrated into more effective local control strategies is also discussed.

Keywords

Adjuvant chemotherapy · Tyrosine kinase inhibitors · Radiopharmaceuticals · Bone-specific therapies · Cryoablation · Stereotactic body radiotherapy (SBRT) · Abscopal response · Immune therapy · Antibodies · Immune modulators · Cell therapy · CAR-T-cells

D. R. Reed (✉)
Cancer Biology and Evolution Program, Adolescent and Young Adult Oncology Program, Department of Interdisciplinary Cancer Management and Sarcoma Department, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA
e-mail: damon.reed@moffitt.org

P. Hingorani
Department of Pediatrics, U.T. MD Anderson Cancer Center, Houston, TX, USA
e-mail: phingorani@mdanderson.org

P. M. Anderson
Cleveland Clinic, Pediatric and Taussig Cancer Institutes, Department Pediatric Hematology/Oncology and BMT, Cleveland, OH, USA

Case Comprehensive Cancer Center, Cleveland, OH, USA
e-mail: andersp@ccf.org

Relapsed Osteosarcoma

Because of the significant resources required to conduct a study and the hundreds of patients needed to answer a question in the newly diagnosed osteosarcoma patient population, most clinical trials are conducted to find an efficacy signal in relapsed patients [1]. Relapsed osteosar-

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coma remains challenging to treat, and patients with relapsed disease have poor overall survival of less than 20% at 5 years. The main predictors of survival after osteosarcoma recurrence include the time to first recurrence, disease burden, and ability to achieve complete surgical remission (CR) after recurrence [2, 3]. Solitary pulmonary nodule and greater than 24 months to the first recurrence are favorable prognostic factors. The Cooperative Osteosarcoma Study Group (COSS) data on patients with first osteosarcoma relapse and those with second and subsequent relapses suggest that the median time to the first relapse is 18 months from the time of original diagnosis. Other studies have suggested this time interval to be 15 months from the original diagnosis. The median time to second relapse from the first relapse is around 8 months, and all subsequent relapses are 6 months. Five-year overall survival rates for patients with the first relapse who are able to obtain a second surgical remission were reported at 39% as compared to 32% for patients who are able to achieve a third surgical remission in the COSS data. Data from the Rizzoli Institute reported 5-year event-free actuarial survival of 38% after first metastasectomy and 32% after second metastasectomy suggesting that patients who achieve a complete resection after second relapse have the same probability of surviving as compared to patients who achieve a complete resection after first relapse [4]. While rare survivors of unresectable disease were reported in this series together, these data point to the fact that the most important factor for survival after pulmonary relapse is the ability to achieve a complete surgical resection.

Past Relapsed Trials and a Proposed Efficacy Bars

An analysis of several prior Children's Oncology Group (COG) phase 2 trials that included patients with recurrent OS showed that patients with unresectable or measurable disease had a 4-month event-free survival (EFS) of 12% (CI 6–19%), while patients with complete resected disease had a 12-month PFS of 20% (CI 10–34%) [5]. This data helped to determine a baseline for outcomes for the design of future trials in patients with relapsed OS as objective response is uncommon in this disease and is, therefore, not a good measure of efficacy of a novel agent. Thus, recent trial designs through COG have focused on two distinct populations of relapsed patients: those with resectable disease and those with unresectable disease. This strategy is also being used on a more global scale with investigators recognizing that RECIST response is not an adequate marker for response in OS.

Using the above historical controls of EFS as a comparator, COG has conducted four clinical trials in the recurrent OS since 2012 (Table 8.1). Two of these trials, AOST1322 and AOST1521, were conducted only in patients with measurable disease, while AOST1421 was conducted only in patients with completely resected pulmonary disease. AOST1321 was unique in having both the above cohorts, which were analyzed separately. While all four agents failed to meet the set efficacy bars for consideration to be studied in a larger Phase 3 trial, several important lessons were learned. These study designs required small numbers of patients (19–39) to evaluate the first efficacy signal. Accrual rate was significantly greater than anticipated based on historical data for these national osteosarcoma-specific trials highlighting an unmet need for relapsed patients [6]. As a result, resources required to conduct these studies were limited and ideal in a resource-constraint environment. In addition, the majority of these trials had novel correlative biology objectives, which will potentially help identify new biomarkers in OS.

Another class of agents that has been studied extensively in OS by investigators outside of COG includes multi-tyrosine kinase inhibitors (TKIs) such as sorafenib, regorafenib, cabozantinib, lenvatinib, and apatinib. While all of these TKIs have a varying profile of targets, most of them met their individual study's efficacy bar of improving progression-free survival (PFS) in OS patients (Table 8.1). Seemingly inhibition of angiogenesis pathways seems to play some role in the observed activity with all members inhibiting VEGF having some activity and saracatinib

Table 8.1 Recently completed trials

Drug trial number/name mechanism/ target	Primary endpoint	Progression-free survival (PFS)	Objective response rate (ORR)
Measurable disease			
Eribulin [8] NCT02097238/AOST1322 Microtubule inhibitor	4-month PFS in >/= 5/19 patients AND >/= 2/19 RECIST response	mPFS 38 days; 0% 4-month PFS	0%
Glembatumumab [9] NCT02487979/AOST1521 Antibody drug conjugate against glycoprotein non-metastatic B protein	4-month PFS in >/= 5/19 patients AND >/= 2/19 RECIST response	4-month PFS 3/19 patients	1/19 patients PR
Denosumab NCT02470091/AOST1321 RANK ligand antibody	4-month PFS in >/= 5/19 patients	4-month PFS 1/15 patients	0%
Sorafenib [10] NCT00889057 VEGFR, PDGFR, Raf	4-month PFS	4mo PFS 46%	ORR 8%
Lenvatinib [11] NCT02432274 VEGFR (1-3), FGFR (1-4), PDGFRα, KIT, RET	4-month PFS	4-month PFS 33% mPFS 3.4 mth	ORR 8%
Regorafenib [12] NCT02389244/REGOBONE VEGFR, TIE2, KIT, RET, Raf, BRAF, PDGFR, FGFR	PFS	mPFS 16.4 weeks; 12 week PFS 62% 24 week PFS 35%	ORR 8% (2 PR)
Regorafenib [13] NCT02048371/SARC024	PFS	mPFS 3.6 months	ORR 14%
Cabozantinib [14] NCT02243605 VEGFR-2, MET, AXL	6-month PFS; 6-month ORR	mPFS 6.2 months;	ORR 12%;
Apatinib [15] NCT02711007 VEGFR2	4-month PFS; ORR at 3 months	mPFS 4.5 months	ORR 43%
Completely resected disease			
Denosumab NCT02470091/AOST1321 RANK ligand antibody	>/= 2/19 RECIST response 12-month DCS of >/= 15/39 patients	Results pending	
Dinutuximab + GM-CSF NCT02484443/AOST1421 Anti-GD2 antibody	12-month DCS of >/= 15/39 patients	Results pending	
Saracatinib SARC12 NCT00752206	12-month DCS	Results pending	

notably not having an activity (personal communication), albeit studied in the resected population [7]. Taken together, these data are intriguing and worthy of further study in a definitive Phase 3 trial in OS. However, it remains a challenge to know which if any of the targets for TKIs are the most important to inhibit biologically, and this remains to be further determined.

Having discussed recently completed trials in the relapsed population, we turn to currently open clinical trials as well as discussions of optimizing clinical trial participation through effective communication to patients and families with recurrent osteosarcoma along with maximizing quality of life through supportive care.

Current Landscape of Clinical Trials in OS

Table 8.2 lists many varieties of clinical trials currently open for osteosarcoma. The majority of these are early phase trials (Phase 1 or 2) with OS cohorts included in them and have varying eligibility criteria as well as efficacy endpoints. While data from these trials will be immensely helpful, a more concerted and unifying approach is needed internationally to design OS-specific trials to truly have an impact on improving survival.

Clinical Trial Participation

While participation in an available clinical trial is the preferred strategy in most instances with relapsed or progressive disease, several factors need to be taken into consideration before enrolling a patient on to a clinical trial as participation in a trial requires significant commitment of time and resources both from the patient/family and the treating institution. Some features worthy of discussion before making an informed decision to participate in a clinical trial include ensuring that participants understand that participation in

Table 8.2 Open clinical trials for relapsed osteosarcoma

Name/agent(s)	Mechanism of action/other information	NCT Identification#
Energy Therapies		
153-Sm-DOTA + RT	Bone-seeking beta-emitter +radiotherapy	NCT03612466
CLR131 (131-iodine)	tumor selective 131-phospholipid ether	NCT03478462
SBRT for oligo-metastases	Stereotactic body radiotherapy	NCT02880319
MRI-guided HIFUS	heat with high-intensity focused ultrasound	NCT02076906
Cytotoxics and/or targeted agents or combinations		
Simvastatin +Topo + CPM	Statin + topoisomerase inhibitor + alkalytor	NCT02390843
Copanlisib	PI3K inhibitor	NCT03458728
Losartan + sunitinib	Angiotensin receptor blocker+ TKI (antiVEGF)	NCT03900793
Nab-paclitaxel + Gemcitabine	More dose dense than gemcitabine+ docetaxel	NCT02945800
Hydroxychloroquine +G/D	inhibit autophagy to reduce G/Dresistance	NCT03598595
Pazopanib + Topotecan	VEGF inhib+ topoisomerase inh	NCT02357810
MM0398+Cyclophosphamide	liposomal irinotecan + alkalytor	NCT02013336
Pediatric MATCH	COG APEC1621SC	NCT03155620
Cabazanitib	TKI (like pazopanib) COG ADVL1622	NCT02867592
Decitabine + gemcitabine	hypomethylation of DNA + gemcitabine	NCT02959164
Antibodies or immune stimulating agents		
Natalizumab	Macrophage-tumor interaction/ICAM	NCT03811886
Avelumab	Anti-PD1 (checkpoint inhibitor)	NCT03006848
Pepinemab (VX15/2503)	AntiSema4D COGADVL1614	NCT03320330
Nivolumab + Nab-rapamycin	Anti-PD1 + mTOR inhibition	NCT03190174
Mifamurtide +EI or M-API	Macrophage activator + standard chemo	NCT03643133
Nivolimab +/− azacytidine	Anti-PD1 +/− histone hypomethylation	NCT03628209
Anti-GD2 x Anti-CD3	Bispecific MAB (increase tumor=T-cell)	NCT03860207
Nivolumab +/− ipilimumab	Dual checkpoint inh. (COGADVL1412)	NCT02304458
Cellular therapies		
EGFR806 CAR-T	Cellular immune therapy with markers	NCT03618381
GD2 CAR-VSV-CTL	Cellular therapy against GD2	NCT01953900
T-cell+anti-CD3+GD2	Bi-specific MAB on T-cells+ IL-2 + GM-CSF	NCT02163093
Donor NK + Haplo BMT	Flu+CPM+3Gy TBI, then HSCT, d+7NK	NCT01200891
Biology Studies		
BOOST	Osteosarcoma Registry and Biobank	NCT03225872

trials is voluntary. They should prepare for success (the trial works to reduce disease) or failure (some or all metastases do not respond) by reviewing the main goals of the trial, i.e., safety, dose finding, or efficacy. Another way to make certain that a decision is informed is to have indications, risks, and alternatives reviewed by another physician or second opinion, especially when local sarcoma expertise is lacking. Sometimes virtual visits can provide a reasonably efficient and effective means of providing a second expert opinion for the patient in terms of prognosis and all potential options applicable to a specific case when the local caregiver may not be fully aware of all trial options [16].

If possible and if in the patient's best interest, some local control measures can be done before clinical trial participation in order to have the best chance of an adequate period of observation on clinical trial therapy to determine the efficacy of the treatment being investigated. This may involve unilateral thoracotomy with the removal of metastases on the contralateral side if the trial is not effective especially if oligometastatic disease and years of interval from the last therapy. Another strategy is to biopsy and cryoablate painful lesions or bone (non-measurable) lesions before trial participation. A third strategy is to use stereotactic body radiation therapy (SBRT) for oligometastatic disease and, if the clinical scenario is such that all cannot be treated, leave 1–3 "indicator" lesions to facilitate clinical trial participation.

For the unfortunate situations involving too numerous to count (TNTC) osteosarcoma lung and/or bone metastases, it is important to involve palliative care specialists and have advance directives in place in case of performance and clinical deterioration before starting any additional therapy or a clinical trial with little hope of being successful in the long run. What is best for a particular patient may involve discussion of lifestyle priorities, various options near their home, prior therapy (what worked and did not and for how long), what is needed to stay healthy, and required clinical trial observations. Resources such as lifextraordinary.org website can help families in a study share their story, organize their own care team, and obtain additional financial resources through crowdfunding. This can be critical to reducing anxiety, sustaining prolonged effort, and avoiding "battle fatigue."

Next Steps: Trial Designs and Efforts Toward Improving Outcomes

As discussed, available clinical trials would be prioritized over off-label therapies in almost every relapsed osteosarcoma setting. A recent review in bone sarcomas found general clinical practice across several centers to be rather uniform and identified clear areas of unmet need [17]. To maximize enrollment and to facilitate correlative studies, ideally trials should be designed to match common clinical scenarios. While the objective of trials is to improve survival, this has not been convincingly achieved with recent front line trials [18–20]. Because the biology and underlying vulnerabilities of osteosarcoma have yet to be characterized, trials should facilitate correlative biology and at a minimum attempt to collect relapse tumor specimens to better understand the biology of osteosarcoma. A short interval of neoadjuvant therapy toward a potential resection can be considered in trial design to both evaluate the effect of therapy in terms of clinical response and to enhance an understanding of the effect of therapy on the tumor through correlative science on the resected specimens. Any resected osteosarcoma samples, especially when primary tissue also exists, should be handled in a way that maximizes the potential biologic utility of samples once the diagnostic material has served its purpose for optimal clinical care. This includes not subjecting materials to acid decalcification and when possible freezing tissue is close to the time of resection as possible. Figure 8.1a outlines commonly explored clinical trial scenarios and ongoing biology work in osteosarcoma. Using recently published trial data in OS, we can estimate accrual to be about 50 patients per year in the completely resected population and about 80 patients per year in the unresectable group [6].

Given the above, what are the current roadblocks and best ideas to overcome them in the osteosarcoma field regarding clinical trials?

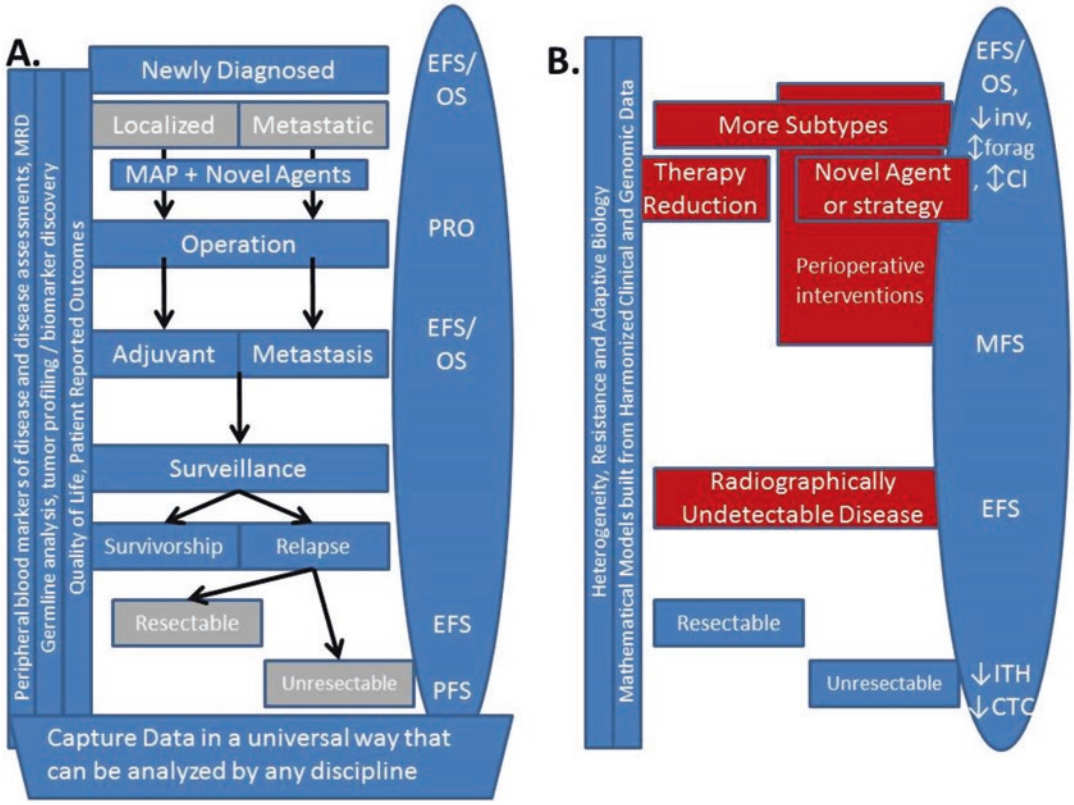

Fig. 8.1 Osteosarcoma clinical scenarios and correlate work in current and potential future trials. (**a**) Current clinical scenarios for trials are the gray boxes in newly diagnosed and relapsed populations typically investigating the addition of an agent to MAP or testing an agent in an unselected relapse population against a historical endpoint. (**b**) New potential directions for trials deign in red along with novel endpoints. Vertical boxes in both A and B highlight ongoing biology efforts highlighted from working groups and being collected on active trials. Ongoing liquid biopsy work may provide an opportunity to better define a complete response, and ongoing aggregation of clinical and biologic information may allow for subtyping of osteosarcoma beyond localized and metastatic. With improved detection and measuring of the MRD state, both novel scenarios and endpoints can be envisioned in future osteosarcoma work. (Abbreviations: ITH intra-tumor heterogeneity, inv invasiveness, forag foraging, CI chromosome instability, MFS metastasis-free survival, CTC circulating tumor cells, PRO patient-reported outcomes)

Several groups have assembled to tackle this question. This has included bringing together members of the basic science, pathology, veterinary, clinical, translational, murine modelers, radiation oncologists, surgeons, and advocates through various venues. Some of these working groups have reported their findings and conclusions. A combined QuadW, Curesearch Foundation, and COG sponsored meeting concluded that paucity of relapsed tumor biology, lack of prognostic markers, and lack of predictive model systems were the key translational knowledge gaps. The group furthermore proposed circulating tumor DNA studies, determining germline genetic abnormalities in osteosarcoma patients and creating patient-derived xenograft models using metastatic and relapsed tumor specimens as the ways to close these gaps [21]. An ongoing European sarcoma networking meeting reported the importance of AYA enrollments in 2011, summarized the 2015 workshop, and conducted a timely meeting in May 2019. The 2015 report highlighted the promising fields of genomics,

drug resistance and pharmacogenomics, translational efforts, and immunotherapy [22]. With the myriad of stakeholders present at this meeting, there was a better understanding of how basic science insights could impact future trials and how trials can best improve tissue sample access for scientific discovery as an example of how trials could be more innovatively designed. In addition, there is increasing recognition between the North American and European investigators that there is an urgent need for data harmonization across all groups to be better able to collaborate on and compare clinical trial outcomes across studies which is a big limitation currently.

While the optimism exudes from these meetings with hopes for a near-term discovery to be translated into positive clinical trials, continuing to better understand the underlying biology of the disease is ultimately needed to design and conduct more effective trials. Toward this effort, several recent publications have emerged on investigating copy number change as predictive to response of targeted agents [23], enhancer regions pliancy contributing to metastatic disease [24], TP53 mutation type being important in metastatic potential [25], and single-cell sequencing that can capture genetic changes, even that from chemotherapy, over time in osteosarcoma [26]. While groups have published sequencing results in osteosarcoma, the largest effort, TARGET, remains in the analytic stage with data available to researchers but lacking a comprehensive manuscript [27]. In addition, the Children's Oncology Group's Osteosarcoma Biology Group, an international group of over 50 researchers that share unpublished data through monthly webinars, devised provocative questions that could help focus research toward questions that would be transformative if answered. These questions included disease ontology including inherited predisposition and osteosarcoma initiation events that lead to the tremendous structural variations that characterize the disease. The underlying biology of established tumors through epigenetic states of osteosarcoma, mechanisms of metastasis, and immune evasion was also highlighted. Finally, characterizing the best predictive models of the disease and optimizing clinical trial designs were highlighted in the final seven provocative questions [28]. Furthermore, there is a general hope that subtyping of osteosarcoma, either through genetic characteristics or phenotypic characteristics, may be helpful in future trials.

Clinical trial design is another important consideration in OS to ensure the efficacy endpoints are relevant to this disease. Due to limited patient numbers with relapsed or progressive disease, only the most compelling novel therapeutic agents can be studied at any given time. Therefore, it is important to consider how to best answer the objective within the context of specific clinical trial design. Importantly, while the importance of metastasis biology has been emphasized for years in osteosarcoma, it remains an aspiration to design a trial with metastasis prevention as an endpoint. This is due to this endpoint being difficult to measure in an unselected osteosarcoma population. The preclinical criteria emphasized to prioritize agents through a past working group included the target being identified in micrometastases, activity in murine tail vein metastasis models, thresholds of metastasis-free survival in canines when given as monotherapy (8-month delay) or with chemotherapy (24 months) and a defined human dose and schedule in addition to activity in comparative oncology models like canines [29].

As specific agents and pathways are discussed at length elsewhere in this book, we focus on conceptual future trial considerations. In addition to potential novel clinical scenarios to conduct trials outlined in Fig. 8.1b, we discuss how advances in technology and understanding may impact future osteosarcoma trials. In Table 8.3, we capture some current thoughts and potential future directions depending on the answers to questions like these: Is the MAP backbone permanent? When should chemotherapy be timed around surgery? How to test agents that only target early metastasis? What will advances in MRD mean for trials? Should immune therapy be incorporated? How to test ideas preclinically and how much dependence on results in models? Which models?

Table 8.3 Possible future directions and impacts on osteosarcoma trials

	Current state	Path forward	Impact on trials
Standard of care	Off-label use common, trial enrollment preferred	Off-label use captured, trials and real-world data inform next trial	Decentralization of ideas for trials. Increased ability of individuals and advocates to test ideas.
Data	Silos of data, much unusable in EHR	International collaboration to harmonize important data elements in a trial as well as outcome measures	Decentralization of background data for trials Allows seamless collaboration on future clinical trials in both patient accruals and outcome comparisons
MAP	Rigidly applied in with little regard to toxicity and risk(s)	Timing, number of cycles may vary between patients depending on the response, agents matched to other therapies or MAP +additional therapies. Some patient with surgery only	More variety in approaches and need to collect information to compare.
Surgery timing	Week 11	Varies with standardized handling and collection of samples	Correlates and biology studies can impact design
Trial designs	Clear bars for efficacy and working toward phase 3 to improve cure rates in the newly diagnosed population	Adopt more nimble trial designs that require fewer patients and resources and allow for changes during a trial based on real-time data; think beyond safety and efficacy, engage basic scientists early in trial design to incorporate relevant biological correlates; include quality of life measures	Allows for more efficient processes such as rapid start, fewer interruptions, addition, or deletion of different trial arms as needed ultimately leading to more data with less resources; learn from even negative trials
Tumor biology	Imperfect understanding of the initiation and targetable drivers of osteosarcoma	Identifying the high impact gaps in tumor biology knowledge; collaborate to share ideas and resources between scientists early in the process	Foster rapid discovery of novel biomarkers and targets with clinical relevance and avoid duplicative efforts
Metastasis biology	They are already there, MAP	Osteosarcoma is dynamic and therapy around the time of surgery may be particularly effective	Interventions and endpoints to detect activity for agents that are not cytotoxic
MRD Threshold	CT scan, 3–5 mm in lung. Higher thresholds by MRI, plain films or bone scan	ctDNA, miRNA, or other peripheral fluid-based technology with improved sensitivity and specificity	More decision points and more possible time points for intervention. Complicates intervention, conduct, and power
Immune therapy	Aspirational	Has a role in selected patients	How to combine immune approaches with surgery, radiation, and chemotherapy rationally?
Models	Available and investigated	A standard suite of well-characterized and freely available models known to predict clinical trial outcomes	Preclinical and comparative studies designed in the context of the planned trial. Correlative biology conducted preclinically focuses on the trial design and interpretation of both positive and negative results.
Stakeholders	Active voice and provide resources and direction. Multiple groups working in parallel with early collaborative efforts.	Break down academic, industry, and nonprofit silos to work as a large team together for the development of new agents for clinical use; foster public-private partnership; involvement of patient advocacy early to in the process of drug development	Rapid bench to bedside translation if academia and industry work together from an early stage; focused drug development for pediatric cancers; better drug availability

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